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Short communication

Buprenorphine infrequently found in fatal overdose in New York City

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ABSTRACT

Background: Buprenorphine is an opioid agonist medication that is both safe and effective in the treatment of opioid use disorders and the prevention of opioid overdoses. Despite this, media coverage has highlighted public concerns about the potential safety consequences of buprenorphine misuse and diversion. To address the possible contribution of buprenorphine to overdose mortality, we systematically tested post mortem blood specimens from decedents who had died of an unintentional drug overdoses in 2013.
Methods: We retrospectively tested consecutive drug overdose cases that occurred from June through October 2013. Cases with available blood specimens were tested for buprenorphine and norbuprenorphine using liquid chromatography-tandem mass spectrometry. Toxicology results were linked to death certificates and case files from New York City Vital Statistics and New York City Office of the Chief Medical Examiner.
Results: Of the 98 unintentional drug overdose fatalities tested, only 2 (2.0%) tested positive for buprenorphine metabolites. All 98 unintentional fatalities involved multiple substances.
Conclusions: Buprenorphine was infrequently found in drug overdose deaths in New York City. Since the safety and efficacy of buprenorphine are well documented, and overdoses resulting from buprenorphine treatment or diversion are very rare, facilitating access to buprenorphine treatment is strongly recommended.

1. Introduction

Opioid agonist therapy (OAT) in combination with counseling or psychotherapy is the most effective treatment for opioid use disorders (American Society of Addiction Medicine, 2014; World Health Organization, 2009). Buprenorphine, an opioid agonist medication, is effective in both treating opioid use disorders and preventing opioid overdose. The safety and efficacy of buprenorphine have been well documented (Bell et al., 2009; Ducharme et al., 2012; Fiellin et al., 2014; Kakko et al., 2003; Kraus et al., 2011; Ling et al., 2012; O'Connor et al., 1998; Orman and Keating, 2009), but popular media accounts highlight public concerns about the potential for and impact of diversion on health and safety (Cicero et al., 2007; Johnson and Richert, 2014; Yang et al., 2013; Yokell et al., 2011; Wish et al., 2012).

In 2013, nearly 100,000 buprenorphine prescriptions were filled by an estimated 14,000 New York City (NYC) residents (New York State Department of Health Prescription Monitoring Program, unpublished data, February, 2015). Recent studies have documented buprenorphine misuse (Bazazi et al., 2011; Genberg et al., 2013) and an increase in buprenorphine-related emergency department (ED) visits (Substance Abuse and Mental Health Services Administration (SAMHSA), 2013). However, buprenorphine-related ED visits represent a small proportion of all drug-related ED visits (Substance Abuse and Mental Health Services Administration (SAMHSA, 2013)), and are typically associated with patients' self-management of withdrawal symptoms (Bazazi et al., 2011; Furst, 2013; Gwin Mitchell et al., 2009), attempts to cease illicit drug use (Schuman-Olivier et al., 2010), or experience of adverse reactions during buprenorphine initiation (Lofwall and Havens, 2012).

Previous research has demonstrated that buprenorphine mortality is rare (Auriacombe et al., 2001; Bretteville-Jensen et al., 2015). In documented cases, buprenorphine-involved mortality is associated with combined use of central nervous system

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depressants (e.g., alcohol, benzodiazepines), rather than attributed to buprenorphine alone (Häkkinen et al., 2012, 2014; Kintz, 2001; Wikner et al., 2014). In NYC, decedents are not tested systematically for buprenorphine, so its impact on mortality may be underestimated, given rising rates of reported diversion. During 2007–2012 in NYC, prior to the study period, seven decedents tested positive for buprenorphine among 3807 unintentional drug poisoning (overdose) fatalities (New York City Department of Health and Mental Hygiene, unpublished data, November, 2013). All deaths were attributed to other substances. During this time, however, testing for buprenorphine was performed based on clinical suspicion and case history, not systematically performed post-mortem. To further investigate the possible contribution of buprenorphine to unintentional drug poisoning (overdose) mortality, the present study examined systematically whether persons who had died from a drug overdose in 2013 had evidence of buprenorphine or its metabolite in their blood. Systematic testing of biological specimens can accurately evaluate the impact of buprenorphine on overdose mortality to provide critical information about the safety of buprenorphine, whether prescribed or used illicitly.

2. Materials and methods

This study was conducted in collaboration with the NYC Office of the Chief Medical Examiner (OCME), a centralized medical examiner system serving the entirety of NYC—over 8 million people. The NYC OCME reviews an estimated 12,000 cases annually of the more than 50,000 deaths in NYC; OCME performs approximately 5500 autopsies. All suspected drug overdoses are referred to the medical examiner for investigation. Determination of death due to drug overdose is based on scene investigations, autopsies, decedent medical histories, and toxicology findings.

In November 2013, we constructed a retrospective sample of the 100 consecutive drug overdose deaths available at that time. Ultimately, because of lag time in case finalization, these deaths represented 31% of the 331 unintentional drug overdose deaths occurring between June 1 and October 31, 2013. Cases with available specimens were sent for testing by an outside commercial laboratory. Testing for buprenorphine metabolites was funded by the NYC Department of Health and Mental Hygiene as part of public health overdose surveillance. Samples were tested for buprenorphine and its metabolite, norbuprenorphine, with reporting limits at 1 nanogram/milliliter using liquid chromatography-tandem mass spectrometry. We linked toxicology results to death certificates from NYC Vital Statistics and case files from the NYC Office of Chief Medical Examiner. Data was analyzed using SAS 9.2 (SAS Institute, Cary, NC, USA). This study was considered routine public health overdose surveillance and not subject to institutional board review.

3. Results

There were 104 drug overdose deaths identified; two did not have specimens available, leaving 102 cases tested for buprenorphine and norbuprenorphine; four cases were determined as undetermined manner of death and excluded from the analysis. Thus, of the 104 samples, 98 (94%) met the criteria for analysis. All 98 unintentional fatalities involved multiple substances (Table 1). Two of the 98 cases (2.0%) tested positive for the buprenorphine metabolite, norbuprenorphine, and additional substances. Both decedents also tested positive for the following three metabolites, 6-monoacetylmorphine, morphine and codeine, the presence of which is consistent with heroin-involved overdose. One case also tested positive for cocaine metabolites, and the other tested positive for both benzodiazepines and opioid analgesics.

Table 1
Post mortem toxicology[1] findings in unintentional (accidental) drug overdose deaths, NYC, June–October 2013.

	Cases (%) $N = 98$
Toxicology by drug type	
Norbuprenorphine	2 (2)
Heroin[2]	57 (58)
Cocaine	41 (42)
Ethanol	38 (39)
Benzodiazepines	29 (30)
Methadone	20 (20)
Opioid analgesics	18 (18)
Sedatives/Hypnotics	13 (13)
Anti-depressants	12 (12)
Anti-psychotics	8 (8)

[1] Toxicology results are not mutually exclusive thus will not add to 100%.
[2] Heroin toxicology as morphine and 6-monoacetylmorphine.

4. Discussion

Our retrospective analysis of a subset of NYC overdose deaths during a five-month period indicates that buprenorphine is rarely present in deaths attributed to drug overdose. The two decedents who tested positive for buprenorphine metabolites also tested positive for heroin metabolites and other substances. The absence of buprenorphine and presence of the buprenorphine metabolite, norbuprenorphine, suggests that the individuals did not recently ingest buprenorphine (Selden et al., 2012). This finding might be consistent with an individual who was receiving maintenance therapy but who may have missed doses. We cannot determine whether these decedents had been prescribed buprenorphine or used non-prescribed buprenorphine for self-management of opioid withdrawal or for other reasons. The finding of concomitant heroin metabolites could be consistent with relapse, which is common, despite treatment.

While the results of our study and prior research suggest that buprenorphine plays a minimal role in overdose mortality, popular media accounts have highlighted the risk of buprenorphine overdose and its association with a burgeoning illicit market (Caniglia, 2013; Genis, 2014; Goodnough and Zezima, 2011; May, 2014; Sontag, 2013), contradictory to the extant scientific literature. Although other risks may be minimally associated with buprenorphine diversion, such as pediatric exposure (Hayes et al., 2008), as the present findings indicate, the risk of buprenorphine overdose is extremely low; considering this, the attention by popular media and policy makers to buprenorphine-related overdose may overstate risk (Clark and Baxter, 2013). In fact, the most common reason for buprenorphine diversion was for management of withdrawal symptoms or attempted self-administration of treatment (Bazazi et al., 2011; Fox et al., 2015; Genberg et al., 2013; Schuman-Olivier et al., 2010).

Several studies demonstrated that barriers to buprenorphine treatment can facilitate, rather than mitigate, buprenorphine diversion. For example, nearly two-thirds of syringe exchange program clients in NYC who reported illicit buprenorphine use also reported not knowing where to access buprenorphine treatment (Fox et al., 2015). Additionally, inability to access buprenorphine treatment increased risk of buprenorphine diversion among a sample of prescription opioid misusers (Lofwall and Havens, 2012). In fact, use of diverted buprenorphine dropped by 70% in one study once individuals were able to gain access to treatment (Schuman-Olivier et al., 2010).

In light of our results, there may be opportunities for policy makers and insurance providers to decrease diversion and misuse of buprenorphine by implementing policies that support and improve access to treatment. For example, a recent study found that more than 40% of United States counties do not have a single

prescriber, and that state policies were associated with prescriber availability (Stein et al., 2015). Currently, only physicians can prescribe buprenorphine for the treatment of opioid use disorders, despite the willingness of nurse practitioners and physician assistants to do so (Roose et al., 2008). In addition, physicians who obtain buprenorphine waivers are able to treat a maximum of 30 patients in their first year of buprenorphine provision and a maximum of 100 patients in following years. However, the Recovery Enhancement for Addiction Treatment (TREAT) Act, introduced in the United States Senate in July, 2014 and currently pending vote, would eliminate the patient limit for physicians after the first year of provision and introduce prescribing rights to qualified nurse practitioners and physician assistants, greatly expanding access nationwide (Recovery Enhancement for Addiction Treatment Act, 2014).

Insurance practices may also limit access to buprenorphine treatment. Some states and insurances do not cover buprenorphine treatment, or impose limits to the length of treatment with buprenorphine (American Society of Addiction Medicine, 2013). Even when treatment is available, delays in treatment because of waiting lists to see prescribers, insurance approvals, and other factors, may further worsen treatment outcomes. Increasing timely access to buprenorphine treatment may not only be a safe and effective means of treating people with opioid use disorder, but also a means of reducing diversion of the medication (Schuman-Olivier et al., 2010).

This study was limited to overdose deaths in NYC, and may not be generalizable to overdose deaths in other locations. Our study analyzed only decedents whose cause of death was determined an accidental drug overdose. In addition, we tested a subset of the 331 unintentional drug overdose deaths that occurred during the time period of June 1 to October 31, 2013. Nonetheless, buprenorphine was rare in the subset of cases. Our study could have missed the presence of buprenorphine in other decedents and underestimated buprenorphine prevalence among all deaths in NYC. Additionally, as some detoxification facilities in New York City utilize buprenorphine, it is possible that the decedents who tested positive were exposed to buprenorphine in a detox setting, although we are unable to determine this. Future studies should prospectively test all overdose decedents for buprenorphine to confirm findings.

Our findings show that buprenorphine was rare in overdose deaths in New York City, suggesting that while rates of diversion may be increasing, there is no evidence that the increase in diversion is leading to significant health consequences such as overdose. Considering the significant risk of overdose death from the use of other opioids, policy makers who wish to decrease opioid overdose deaths should consider increasing, rather than decreasing, access to buprenorphine treatment as a response to buprenorphine diversion.

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Contributors

Denise Paone and Ellenie Tuazon had full access to study data and take responsibility for the accuracy of the data analysis. Denise Paone, Hillary Kunins, Barbara Sampson, and Marina Stajic were responsible for study concept and design and critical revision of the manuscript. Denise Paone, Hillary Kunins, and Ellenie Tuazon were responsible for the analysis and interpretation of the data. Bennett Allen and Shivani Mantha contributed to manuscript drafting. All authors approved the final article as submitted on 05 August 2015.

Conflict of interest statement

No conflicts declared.

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